Remarks/Arguments: Interview Summary

The below summarizes a telephone interview conducted with regard to the present application.

On June 1, 2009, Examiner Bruce Hissong, Primary Examiner Gary Nickel, and the below-signed representative Valerie Neymeyer-Tynkov discussed the Amendment filed in this application on May 10, 2009.

Differences between permeation techniques of the state of the art and penetration techniques of the present invention were briefly discussed during the interview, in keeping with discussion provided in the May 10 Amendment, with Ms. Neymeyer-Tynkov directing attention to pages 14 – 16 of the application as filed and noting that Santus and similar state of the art documents depended on smearing chemicals across the nasal mucosa to create passageways for drugs to pass through, while penetrants of the present invention appear to exploit already-existing passageways, thus facilitating drug delivery while avoiding damaging the nasal mucosa.

Also discussed was whether the present claims allow for too many possible lipids and surfactants to be used in a penetrant of the present invention, as penetrants of the present Examples were made only from soybean phosphatidylcholine as lipid and either Tween-80 or sodium cholate as surfactant. Ms. Neymeyer-Tynkov pointed out that other aspects of the claims help to further define penetrants of the present invention, and that those skilled in the art will know how to make penetrants in view of the claims and information provided in the application. Also, Ms. Neymeyer-Tynkov pointed out page 20 of the May 10, 2009 Amendment, which notes that some penetrants of the present invention used phosphatidylglycerol in conjunction with soybean phosphatidylcholine, and used 50% ionized cholic acid as surfactant. Also, Ms. Neymeyer-Tynkov pointed out that the Amendment page 20 notes that the present application expressly incorporates by reference several documents to describe formulations of penetrants of the present invention, and that those formulations refer to several other lipids and surfactants that may be used to make penetrants, including for instance dipalmitoyltartric acid ester and phosphatidylethanolamine-N-fluorescein as lipids, and oleic acid and sodium lauryl sulfate as surfactants.

Examiner Hissong mentioned it would be useful to see how other US Examiners have handled other applications regarding penetrants of the present claims. Applicant's representative advised the Examiner that USPTO prosecution of Application No. 09/890,335, identified at page 1 of the present application, is on-going before Examiner Gangle. Also, Mrs. Neymeyer-Tynkov noted that the US prosecution history of US counterparts of PCT applications mentioned at page 13 of the application as filed may also be useful to the Examiner.

Ms. Neymeyer-Tynkov also noted that the file history of the present invention included several in-depth discussions of the role of didecanoylphosphatidylcholine (DDPC) as a lipid of the present invention. The discussion began with a rejection under 35 U.S.C. 103(a), which included an analysis by the Examiner where DDPC used in Drejer *et al.* (Diabetic Medicine 9:335-340 (1992)) was likened to a lipid of the present invention. In overcoming the rejection, Applicant advised that DDPC was not useful as a lipid of the present invention; thereafter, several discussions of the role of DDPC in the present invention arose in response to related rejections made under 35 USC 112. Ms. Neymeyer-Tynkov pointed out that all rejections relating to DDPC as a lipid have been overcome. However, she wished to

note on record that PCT/EP96/04526, incorporated by reference at page 13 of the application and equivalent to and published as US Publication No. 2002/0048596, Examples 5-6, describe the preparation of carriers with SPC and DDPC where, in the context of the present claims, SPC is a lipid and DDPC is a surfactant. Ms. Neymeyer-Tynkov noted that previous discussion of DDPC in the file history of this application is presumed to be in the context of DDPC as a lipid of the present claims, and not a surfactant. Also, Mrs. Neymeyer-Tynkov noted that Examples 5-6 may support Applicant's previous mention that DDPC is not useful as a lipid in the present invention.

Remarks/Arguments relating to the present Amendment

No new matter is believed to be added by this Amendment.

Regarding amendments to the specification

The amendment to the chemical structure occurring in the paragraph spanning page 26 line 23 to page 27 line 17 is to correct a typographical error occurring within the phosphate group of the pictured chemical structure. Specifically, an oxygen atom is included with the phosphate group pictured as bound to group R_3, so that "P-R_3" is now "P-O-R_3". Support for this amendment is provided in the attached Appendix. While one skilled in the art may presume the presence of the oxygen atom in the structure as currently presented (see for instance a similar representation and typographical error in Mathew-van Holde's Biochemistry p. 303; Appendix), as Applicant is aware of the typographical error, Applicant corrects the error herein. This correction is also supported for instance by the disclosure at pages 26-27 that the structure relates to the class of phospholipids having the formula defined therein. All phospholipids include the inserted oxygen; see for instance the Appendix included herein.

Regarding amendments to the claims

Claims 54 and 100 are amended to refer to "aqueous" liquid medium. Support for the amendment is available throughout the application, and for instance at page 12 lines 30-31 of the application as filed. Applicant notes that this amendment further limits the relationship between the less soluble and more soluble substances identified in claims 54 and 100, so that the solubility difference between the two substances is in terms of each substance's solubility in aqueous liquid medium.

Claim 76 is amended to refer to the solvent of claim 54, so that the supporting medium of claim 76 correctly refers to the medium supporting carriers of the present invention. Support for this amendment may be found for instance at page 29 line 17 to page 30 line 4 of the application as filed. Claim 99 is amended in keeping with US antecedent basis practice. Claim 110 is amended to correct the chemical structure therein; support for this correction may be found as discussed above regarding the correction to the specification, and in the Appendix.

Other Remarks/Arguments

The Supplemental IDS included with the present Amendment includes information relating to the prosecution of other applications that may relate to aspects of the present invention such as penetrant technology. Substantive Office Actions issued in US Appln. No. 09/890,335, in US counterparts to the PCT applications identified at page 13, and other applications are included with the

Appln. No. 09/890,371
Supplemental Amendment dated July 13, 2009

IDS filed in this application on July 12, 2009. Several Office Actions including rejections based on prior art or state of the art documents are pointed out in the IDS for the Examiner's convenience.

* * * *

Applicant respectfully submits that the present Amendment places the present application in better condition for allowance, and respectfully requests that the Examiner allow the application proceed to grant. In the event that the Examiner has any questions or concerns that the Examiner believes may be discussed by telephone, the Examiner is invited to contact the below-signed representative as indicated below.

Respectfully submitted,

July 13, 2009

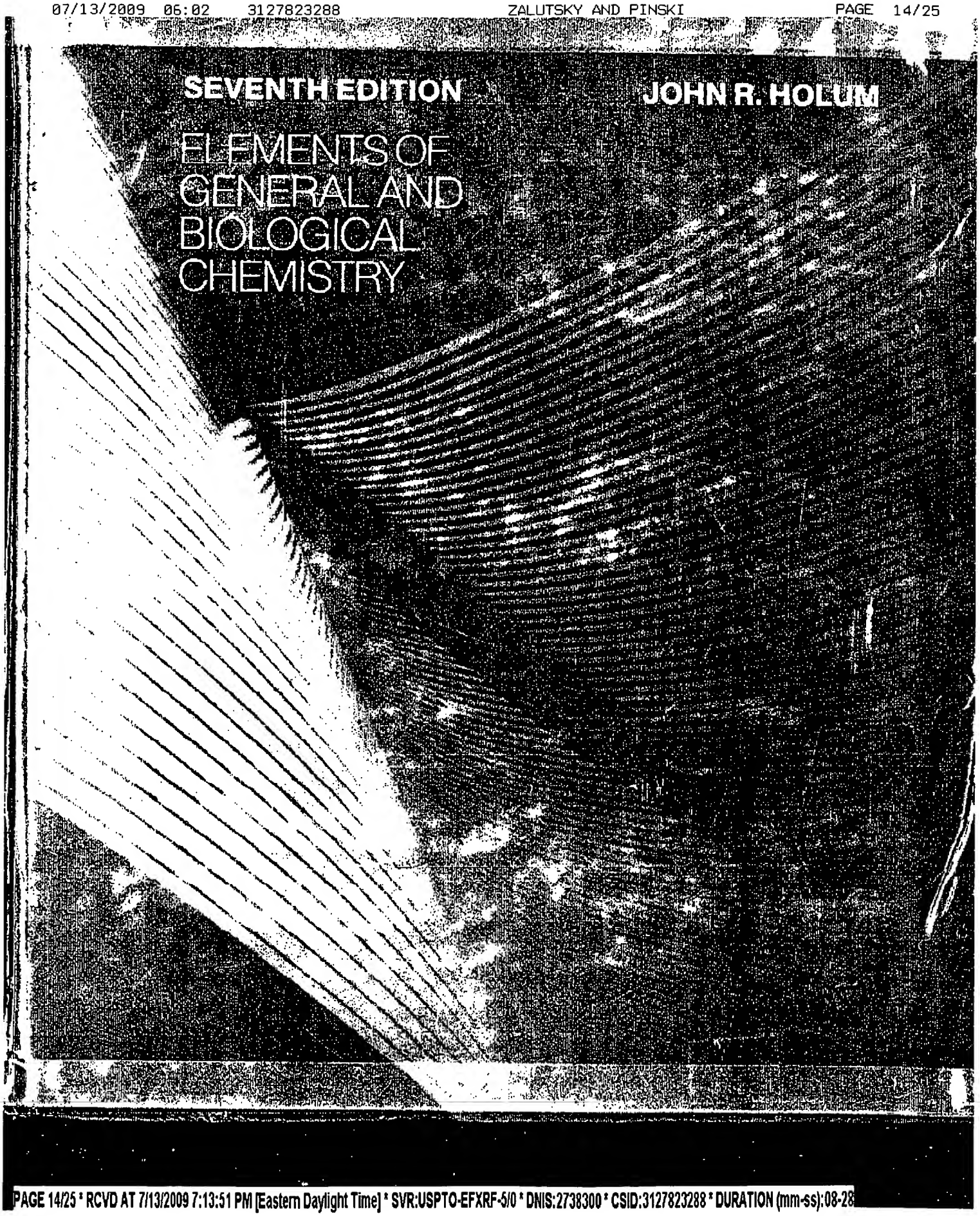
Valerie Neymeyer-Tynkov
Reg. No. 46,956
Neymeyer-Tynkov LLC
20 N. Clark St. Suite 600
Chicago, IL 60602
Phone: 312/965-1969

Appendix

Holum, Elements of General and Biological Chemistry: John Wiley & Sons, USA (1987) – pages 324, 325.

Stryer, Biochemistry: W.H. Freeman and Company, San Francisco, California (1981) – pages 208, 209.

Mathews and van Holde, Biochemistry: The Benjamin/Cummings Publishing Company, Redwood City, California (1990) – pages 303, 304.


SEVENTH EDITION
JOHN R. HOLUM
ELEMENTS OF GENERAL AND BIOLOGICAL CHEMISTRY

Production supervised by Linda R. Indig
Illustrations by John Balbalis with the assistance of the Wiley Illustration Department
Design supervised by Ann Renzi
Photo researched by Stella Kupferberg
Manuscript edited by Vivian Danser under the supervision of Deborah Herbert.
Cover photograph by Paul Silverman

Library of Congress Cataloging in Publication Data:

Holum, John R.
Elements of general and biological chemistry.

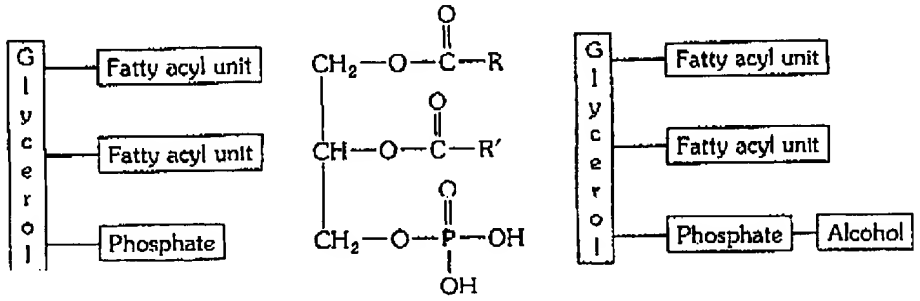
Includes bibliographies and index.
1. Biological chemistry. I. Title.

QP514.2.H64 ' 1987 574.19'2 86-7827
ISBN 0-471-83831-4

Printed in the United States of America

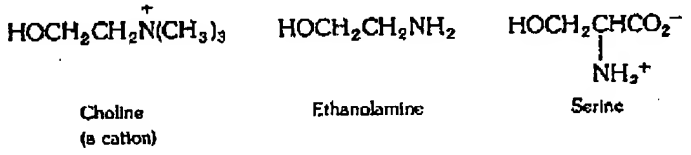
10 9 8 7 6 5 4 3 2 1

joined by a phosphate ester link to a small alcohol molecule. When this link is absent, the material is called phosphatidic acid.

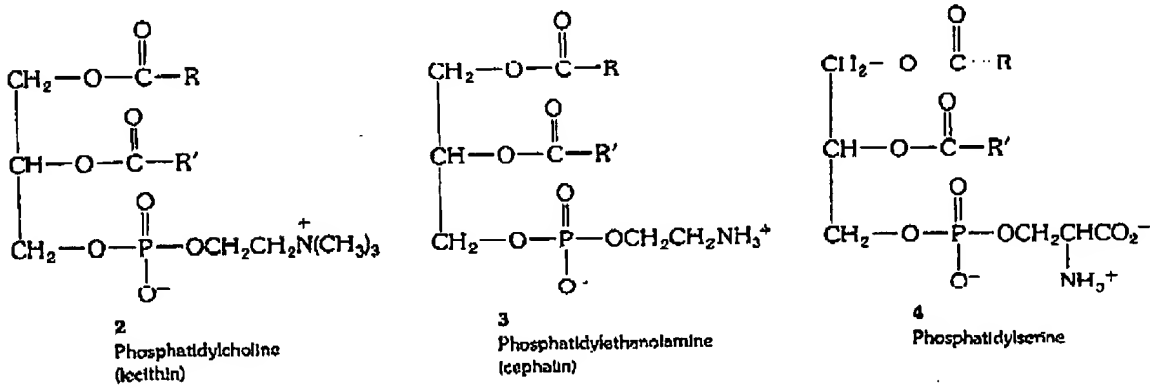


Cephalin is from the Greek *kephale*, head. Cephalin is found in brain tissue.

The three principal phosphoglycerides are esters that are formed between phosphatidic acid and either choline, ethanolamine, or serine to give, respectively, phosphatidylcholine (lecithin), **2**, phosphatidylethanolamine (cephalin), **3**, and phosphatidylserine, **4**.



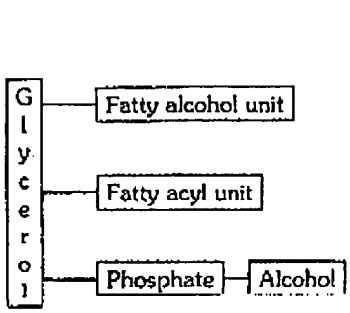
As the structures of **2**, **3**, and **4** show, one part of each phosphoglyceride molecule is very polar because it carries full electrical charges. The remainder is nonpolar and hydrocarbon-like. These characteristics have important implications in understanding how phosphoglycerides are used to make cell membranes (Section 15.5).



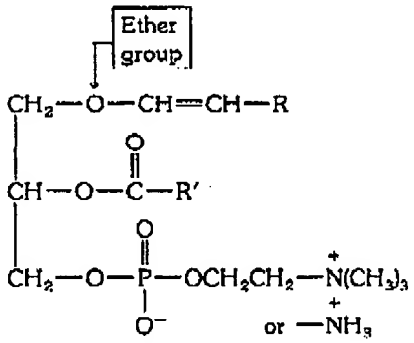
Lecithin is from the Greek *lekitos*, egg yolk—a rich source of this phospholipid.

When pure, lecithin is a clear, waxy solid that is very hygroscopic. In air, it is quickly attacked by oxygen, which makes it turn brown in a few minutes. Lecithin is a powerful emulsifying agent for triacylglycerols, and this is why egg yolks, which contain it, are used to make the emulsions found in mayonnaise, ice cream, custards, and cake dough.

Plasmalogens. The **plasmalogens** make up another family of glycerol-based phospholipids, and they occur widely in the membranes of nerve cells and muscle cells. They differ from the other phosphoglycerides by the presence of an unsaturated ether group instead of an acyl group at one end of the glycerol unit.



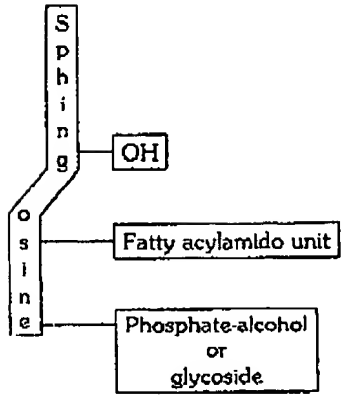
Components of plasmalogens



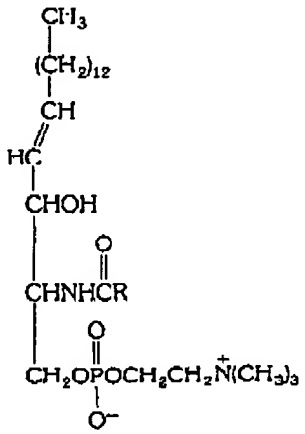
Plasmalogens

Sphingolipids. The two types of sphingosine-based lipids or **sphingolipids** are the sphingomyelins and the cerebrosides, and they are also important constituents of cell membranes. The sphingomyelins are phosphate diesters involving sphingosine. Their acyl units occur as acylamido parts, and they come from unusual fatty acids that are not found in neutral fats.

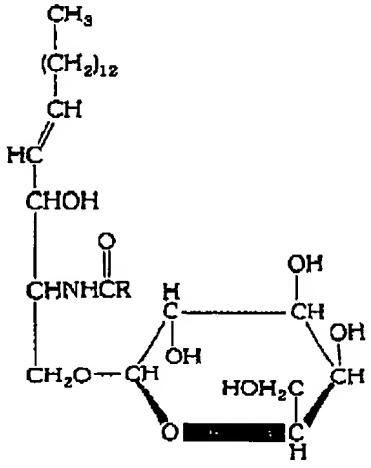
The cerebrosides are not actually phospholipids. Instead they are **glycolipids**, lipids with a sugar (i.e., glycose) unit and not a phosphate ester system. The sugar unit is usually that of D-galactose, or D-glucose, or amino derivatives of these.



Components of sphingolipids



Sphingomyelins



Cerebrosides

Second Edition

BIOCHEMISTRY

Lubert Stryer

STANFORD UNIVERSITY

W. H. FREEMAN AND COMPANY
San Francisco

DESIGNER: *Robert Ishi*
ILLUSTRATOR: *Donna Salmon*
ILLUSTRATION COORDINATOR: *Audre W. Lacerde*
PRODUCTION COORDINATOR: *William Murdock*
COMPOSITOR: *York Graphic Services*
PRINTER AND BINDER: *Arcata Book Group*

Library of Congress Cataloging in Publication Data

Stryer, Lubert.
Biochemistry.

Includes bibliographies and index.
1. Biological chemistry. I. Title. [DNLM:
1. Biochemistry. QU4 S928b]
QP514.2.S66 1981 574.19'2 80-24699
ISBN 0-7167-1226-1

Printed in the United States of America

9 8 7 6 5 4 3

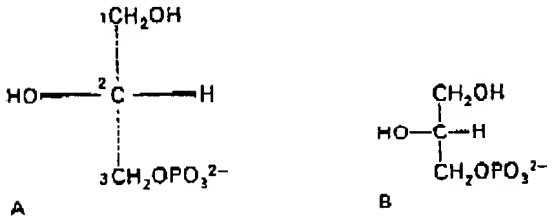
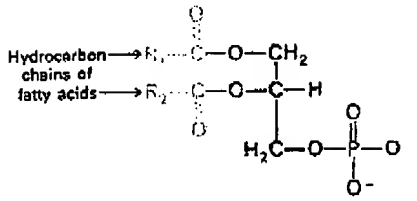
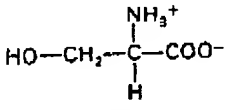


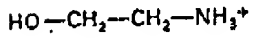
Figure 10-4
Absolute configuration of the glycerol 3-phosphate moiety of membrane lipids: (A) H and OH, attached to C-2, are in front of the plane of the page, whereas C-1 and C-3 are behind it; (B) Fischer representation of this structure. In a Fischer projection, horizontal bonds denote bonds in front, whereas vertical bonds denote bonds behind the plane of the page.

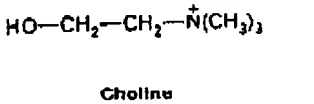
In phosphoglycerides, the hydroxyl groups at C-1 and C-2 of glycerol are esterified to the carboxyl groups of two fatty acid chains. The C-3 hydroxyl group of the glycerol backbone is esterified to phosphoric acid. The resulting compound, called *phosphatidate* (or diacylglycerol-3-phosphate), is the simplest phosphoglyceride. Only small amounts of phosphatidate are present in membranes. However, it is a key intermediate in the biosynthesis of the other phosphoglycerides.

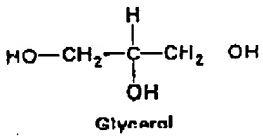


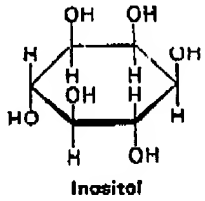
The major phosphoglycerides are derivatives of phosphatidate. The phosphate group of phosphatidate becomes esterified to the hydroxyl group of one of several alcohols. The common alcohol moieties of phosphoglycerides are serine, ethanolamine, choline, glycerol, and inositol.



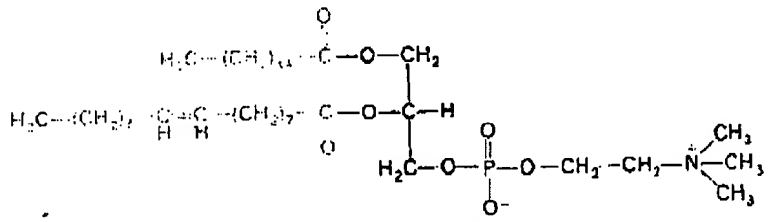








Now let us link some of these components to form phosphatidyl choline, a phosphoglyceride found in most membranes of higher organisms.



The structural formulas of the other principal phosphoglycerides—namely, phosphatidyl ethanolamine, phosphatidyl serine, phosphatidyl inositol, and diphosphatidyl glycerol—are given in Figure 10-5.

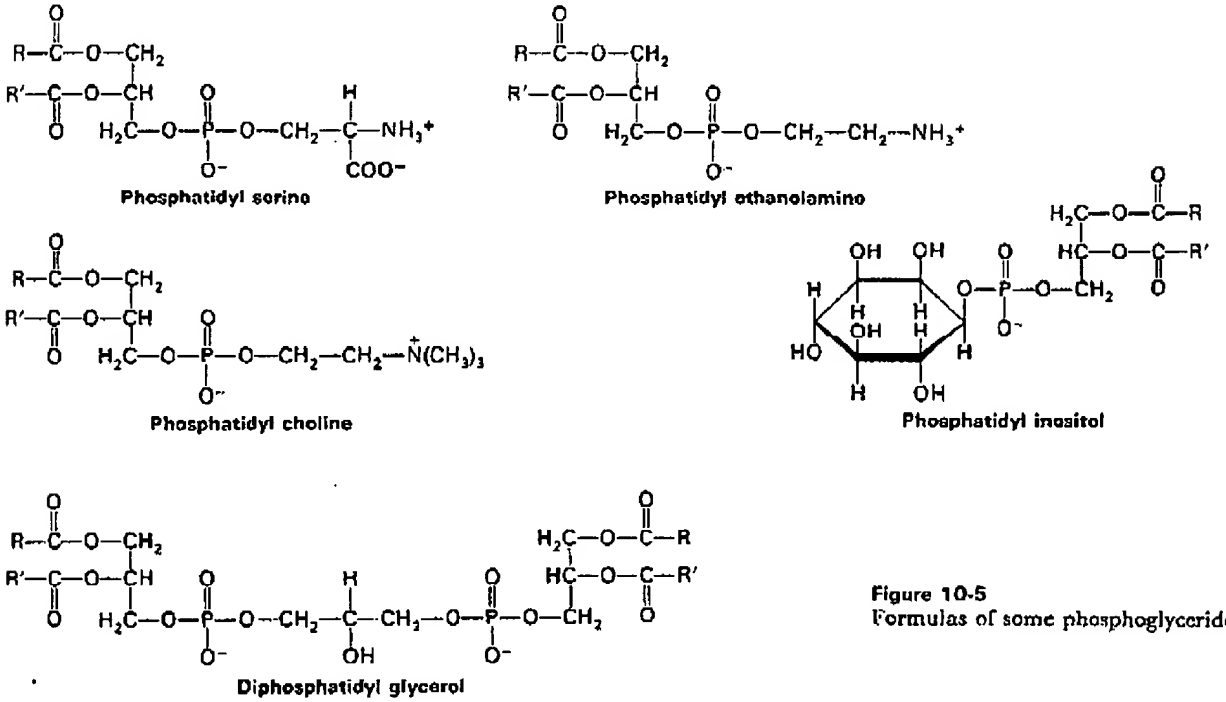
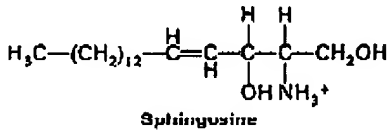
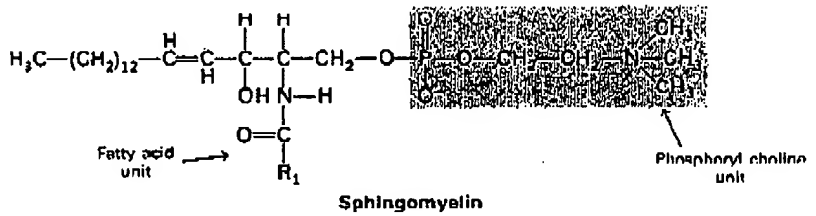


Figure 10-5
Formulas of some phosphoglycerides.

Sphingomyelin is the only phospholipid in membranes that is not derived from glycerol. Instead, the backbone in sphingomyelin is *sphingosine,* an amino alcohol that contains a long, unsaturated hydrocarbon chain. In sphingomyelin, the amino group of the sphingosine backbone is linked to a fatty acid by an amide bond. In addition, the primary hydroxyl group of sphingosine is esterified to phosphoryl choline. As will be shown shortly, the conformation of sphingomyelin resembles that of phosphatidyl choline.





BIOCHEMISTRY

Christopher K. Mathews
Oregon State University

K. E. van Holde
Oregon State University

Illustration concepts by Audre W. Newman
with art contributions from Irving Geis

Cover

Dimer of *trp* repressor protein, with bound tryptophan (in blue). The protein binds to DNA and regulates expression of the *trp* genes that control tryptophan biosynthesis. Crystal structure by Paul Sigler et al.; image by Jane and David Richardson.

Frontispiece

Figure 11.15a The T state of aspartate transcarbamoylase, as determined by x-ray diffraction.

Sponsoring Editor: Diane Bowen
Developmental Editor: Susan Weisberg
Production Supervisor: Anne Friedman
Art Coordinator: Bruce Lundquist
Interior and Cover Designer: Gary Head
Dummy Artist: Wendy Calmenson
Copyeditor and Indexer: Mary Prescott
Principal Illustrator: Georg Klatt
Illustrators: Ken Miller, Elizabeth Morales-Denney, and Irene Imfeld
Proofreaders: Sheila Kennedy and Kathy Lee
Photo Research and Permissions: Rachel Menzi
Typesetter: York Graphic Services, Inc.
Film Preparation: Color Response, Inc.

Library of Congress Cataloging-in-Publication Data

Mathews, Christopher, K., 1937–
Biochemistry/Christopher K. Mathews, K. E. van Holde; illustration concepts by Audre Newman with art contributions from Irving Geis.
p. cm.
Includes bibliographical references.
ISBN 0-8053-5015-2
1. Biochemistry. I. Van Holde, K. E. (Kensal Edward), 1928–
II. Title.
[DNLM: 1. Biochemistry. QU 4 M4294b]
QP514.2.M384 1990
574.192—dc20
DNLM/DLC
for Library of Congress 89-17922
CIP

ISBN: 0-8053-5015-2

CDEFGHIJ-VH- 93210

The Benjamin/Cummings Publishing Company
390 Bridge Parkway
Redwood City, CA 94065

The Lipid Constituents of Biological Membranes

All biological membranes contain lipids as major constituents. The molecules that play the dominant roles in membrane formation all have highly polar head groups and, in most cases, *two* hydrocarbon tails. There is a molecular sense to this: If a large head group is attached to a single hydrocarbon chain, the molecule is wedge shaped and will tend to form spherical micelles (Figure 9.5a). A double tail yields a roughly cylindrical molecule, which can easily pack in parallel to form extended sheets of membranes. As indicated in Figure 9.5b, such membranes will be bilayers, with the hydrophilic head groups facing outward into the aqueous regions on either side. A number of classes of membrane-forming lipids share this type of structure; they differ principally in the nature of the head group. We shall describe a few examples of each.

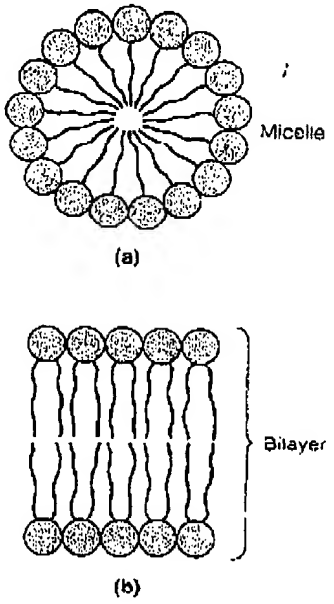


Figure 9.5
How molecular shape of lipids determines the structures they form. (a) The single tail of a fatty acid makes the molecule wedge-shaped, favoring micelle formation. (b) The multiple tails on membrane-forming lipids make the molecules more cylindrical, so that planar bilayer sheets can be formed.

Glycerophospholipids

Glycerophospholipids (also called **phosphoglycerides**) are the major class of naturally occurring **phospholipids**, lipids with phosphate-containing head groups. These compounds make up a significant fraction of the membrane lipids throughout the bacterial, plant, and animal kingdoms. All can be considered to be derivatives of glycerol-3-phosphate. Carbon 2 in glycerol-3-phosphate is a chiral center, and the naturally occurring glycerophospholipids are derivatives of the L enantiomer. The general structure of this group of compounds is shown in Figure 9.6. In panel (a) is depicted the stereochemical configuration. Panel (b) shows the molecule in the manner we will generally use to represent membrane lipids, with the hydrophobic tails drawn to the right and the hydrophilic head group to the left. Usually, R_1 and R_2 are acyl side chains derived from the fatty acids; often one is saturated, the other unsaturated. The R_3 group varies greatly, and it is this that confers the greatest variation in properties among the glycerophos-

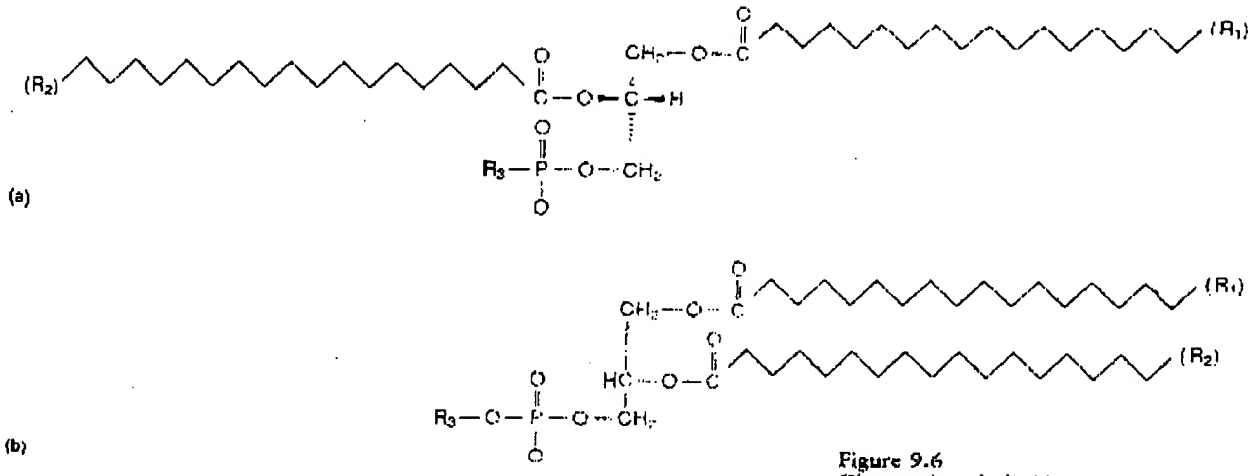


Figure 9.6
Glycerophospholipid structure. (a) Stereochemical view of L-enantiomer. (b) A conventional visualization.

304

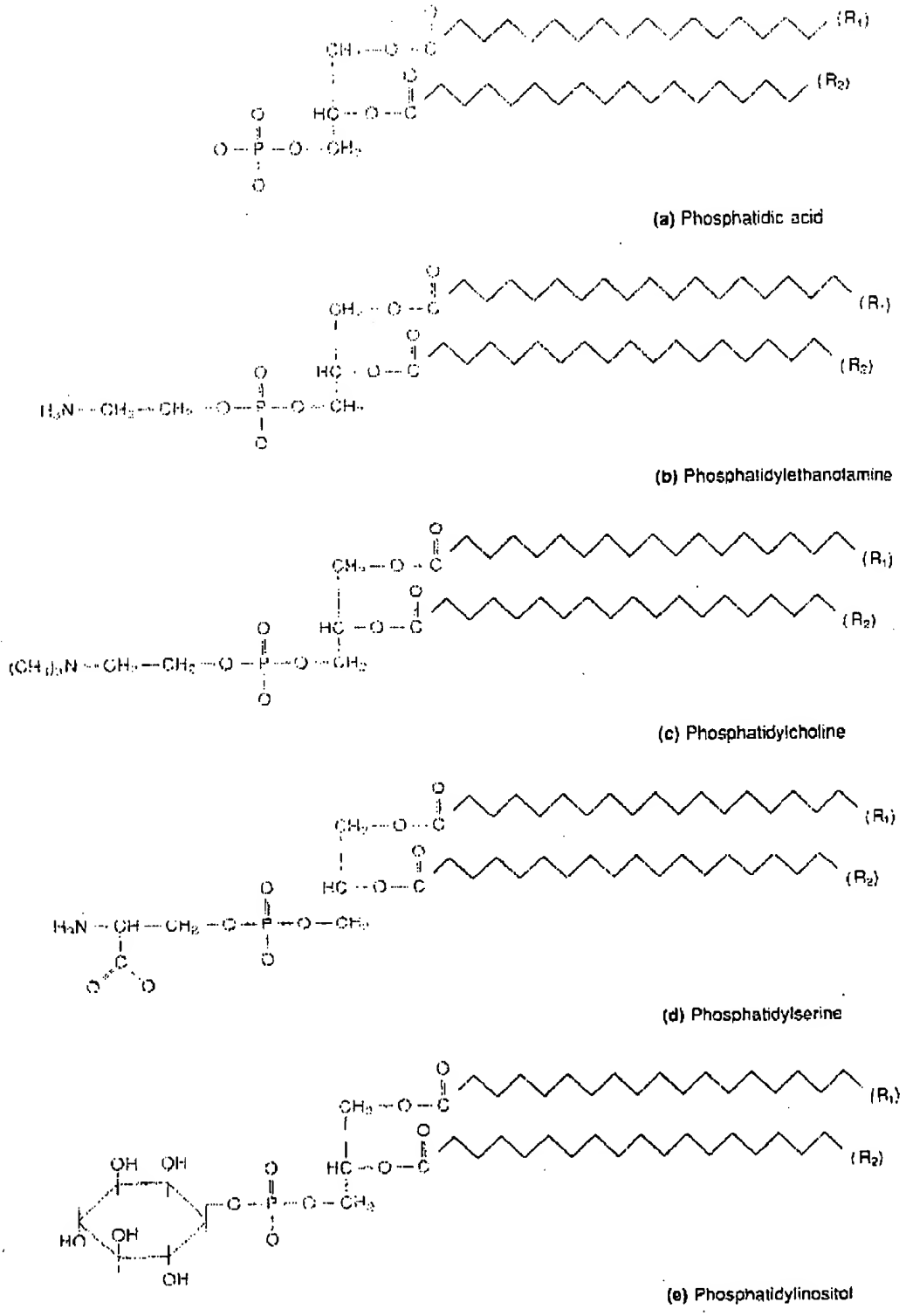


Figure 9.7
Examples of common glycerophospholipids. The hydrophobic R groups are indicated in yellow, the glyceryl moiety in black, and the very hydrophilic head groups in blue. All may be considered derivatives of phosphatidic acid (a).